PHARMACOGENOMICS IN PEDIATRIC PAIN MANAGEMENT MYTH OR REALITY?

Cheryl Mele DNP PNP AC/PC- BC  NNP-BC
I do not have any disclosures nor any relevant financial relationships to disclose.
OBJECTIVES

1. Describe scientific terminology related to pharmacogenomics
2. Identify the specific genes involved in the pharmacodynamics and pharmacokinetics of certain pain management drugs utilized in various pediatric disorders
3. Identify current pharmacogenomics research which applies pediatric pain management
• E. B. is a 20-month-old female admitted for resection of sacrococcygeal germ cell tumor transferred to PICU on post-op day 0 for uncontrolled pain. EB had significant pain issues in the PACU and was started on PCA morphine basal and bolus RN/Mom controlled. She was prescribed benzodiazepines and IV ketorolac to assist with pain control. Her basal rate required a two-fold increase to 30 mcg/kg/h, and morphine boluses were increased by 30% without some relief. With concerns for safety, pain team stated that narcotic dosing could not be increased further without monitoring in an ICU setting.
INTRODUCTION

• Patient’s genetic make-up may account for a considerable disparity in response to treatment or even an adverse drug reaction (ADR)
• ADRs in the U.S. are estimated to cost
• $100 billion annually, form the basis of severe morbidity and mortality issues, and account for 7% of hospital admissions
• Pharmacogenomics has the potential to significantly improve patient outcomes.
• The Food and Drug Administration (FDA) in the US now strongly recommends that genetic testing be performed in children before initiating treatment specifically for cancer, HIV, and anticoagulant therapy

OVERVIEW OF GENETIC BASICS AND PHARMACOKINETICS

• The human genome consists of 23 base pairs of chromosomes that are composed of chunks of DNA.
• The building blocks of the spiral staircase are the four-nucleotide bases.
• DNA base pairs along the chromosome is called the DNA sequence or codon.
• Differences in individual genetic makeup alter the structure or the function of proteins that participate in the key operation of pharmacokinetics.
• Phenotype vs genotype.
CLINICAL APPLICATIONS OF PHARMACOGENOMICS

• Psychiatry
• Pulmonology
• Pain management
• Oncology

FDA Link:
• http://www.fda.gov/drugs/science/research/areas/pharmacogenetics/ucm083378.htm

• Gastroenterology
• Cardiology
• Gerontology
• Infectious Diseases
VARIATION IN DRUG RESPONSE

- Polymorphisms in genes coding for:
  - Metabolizing enzymes
  - Transporters
  - Receptors
- Body Mass Index
- Development
- Tobacco or Alcohol use
- Co-morbid conditions
- Alterations in organ function

Figure 1. Heritable factors influencing drug-organism interaction. Source: American Society of Anesthesiologists, Inc. 39 (p. 302).
GENETIC POLYMORPHISMS

• Genetic Polymorphisms lead to proteins that are:
  • Nonfunctional
  • Super-functional
  • Absent

• Developmental Pharmacogenomics (gene expression)

• Example: CYP 3A 7 are highly expressed in gestation and silenced 1-2 years after birth; CYPA4 are low at birth and increase first months years of life

• Adverse effects
Pharmacogenetics is the study of genetic differences in the alleles associated with individual variability in drug response. Patients with the same diagnosis respond differently because of allelic difference: in this example, the normal gene sequence is GCCCAGGTC but the mutation gene sequence is GCCCAGGTC. The AGC in the sequence of the normal gene codes for serine,
SINGLE NUCLEOTIDE POLYMORPHISM (SNP)

• A normal sequence of genetic bases is substituted
• The gene function is changed and called genetic polymorphism
• Could identify nonfunctional, superfunctional, or absent proteins, which modify a gene's drug coding metabolism enzymes, drug transporters, and receptors
• Collections of SNPs or other different genes are located close to each other on a chromosome; when inherited together, this is called a HapMap or haplotype
Pharmacogenetics is the study of genetic differences in the alleles associated with individual variability in drug response. Patients with the same diagnosis respond differently because of allelic difference; in this example, the normal gene sequence is GCCCAGGTC but the mutation gene sequence is GCCCAGGTC. The AGC in the sequence of the normal gene codes for serine,
METABOLIZING ENZYMES AND GENES

• The Cytochrome P450 enzyme system (CYP450) is found in the liver and is accountable for metabolism of numerous drugs
• An individual's ethnic or ancestral background also influences how CYP genes perform during drug metabolism
• drug metabolism is affected by ontogeny (development
METABOLIZING ENZYMES AND GENES

- The human genome comprises 57 CYP genes which are classified according to sequence homology.
- CYP 1 to 3 genes are involved in phase I drug metabolism.
- CYP 4 to 51 are associated with endobiotic metabolism.
• CYP2D6 is responsible for the metabolism of a number of different drugs
  • Antidepressants, antipsychotics, analgesics, cardiovascular drugs
• Over 100 polymorphisms in CYP2D6 have been identified
• Phenotype varies with ethnicity
EXEMPLAR: CYP3A FAMILY CYP3A FAMILY

- Metabolism of about 50% of medications
  - Calcium channel blockers
  - Benzodiazepines
  - Statins
  - Acetaminophen
- Grapefruit juice is enzyme inhibitor
- St. John’s Wort is enzyme inducer
- Inconsistent genotype/phenotype concordance
PHASE I & II DRUG REACTIONS

- Genetic polymorphism in phase I & II Drug Metabolism
- CYP genes are the most important phase 1 enzymes.
- Phase II enzymes, have multiple alleles with varied expression & include:
  1. arylamine N acetyltransferases (NAT 1, NAT 2)
  2. glucuronosyl transferases (UGTs)
  3. thiopurine S-methyltransferase.

Phase II enzymes add an acetyl group onto a drug to process elimination
Sulfamethoxazole, hydralazine, procanimide, and tuberculosis medications require acetylation to facilitate metabolism
EXEMPLAR: N-ACETYLTRANSFERASE (NAT)

- Phase II liver enzyme
- Adds an acetyl group onto drugs in the process of acetylation
- Sulfamethoxazole, hydralazine, procainamide, isoniazid, and caffeine
- Infectious disease well known differences in isoniazid pharmacokinetics

-**N-Acetyltransferase**: liver enzyme that activates some drugs and deactivates others.
  - slow acetylators may experience toxicity when taking drugs such as procainamide, isoniazid, hydralazine, and sulfonamides
  - fast acetylators may not respond to isoniazid or hydralazine.
- between 40% and 70% of Caucasians and African-Americans are considered to be slow acetylators.
DRUG METABOLISM

- **Active drug**: Capable of exerting the intended action in this form.

- First-stage metabolism forms inactive metabolites.

- **Prodrug**: A precursor (forerunner) of a drug.

- A prodrug must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent.
Depending upon the genetic makeup of the described metabolizing enzymes a person has inherited, they will be categorized:

1. poor metabolizer (PM)
2. intermediate metabolizer (IM)
3. extensive metabolizer (EM)
4. ultra-metabolizer (UM)

Ethnicity plays a role in type of metabolism

prodrug (inactive drug) that arrives in the liver has different dynamics of metabolism than an active drug
PRO DRUG EXEMPLAR: CODEINE

- Codeine requires activation by CYP2D6 in order to exert its analgesic effect
- Due to genetic polymorphisms, 2-10% of the population cannot metabolize codeine and are resistant to the analgesic effects
- Enzyme involved converting codeine to morphine is known to be highly polymorphic
PRO DRUG : CODEINE

• Deaths in children due to codeine highlight the importance of CYP2D6 genetic tests and avoidance of opioids metabolized by the CYP2D6 pathway in ultra rapid and extensive metabolizing children.

• Responses to tramadol and possibly oxycodone and hydrocodone may also be affected by CYP2D6 genotypes though studies are not consistent and therefore more evidence is needed.

• A case report concerning an infant death was alleged to originate by morphine intoxication from breast-feeding. The infant’s blood concentration of morphine was measured at 70 ng/mL vs. more typical concentrations of about 1 ng/mL to 2 ng/mL

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

• NSAIDs are utilized in postoperative pain for their anti-inflammatory properties and metabolized by the cytochrome CYP2C9. The CYP2C9 is highly polymorphic in Caucasian population.

• Some CYO2C9 genes are found to be poor metabolizers and can play a major part in NSAID toxicity. Over the last decade, guidelines have been utilized for patient genotyping testing and adjusting drug dosages with better therapeutic outcomes.

• (Samer, Lorenzini, Rollason, Daali, & Desmeules, 2013); (Ting & Schug, 2016).
Pain perception & genetics

• Pain is a complex neurophysiological condition involving multiple components and their interactions, which is perceived differently among individuals.

• COMT gene serves as a pivotal regulator of dopamine, epinephrine and norepinephrine concentrations in the pain perception pathway.

• Low COMT activity results in elevated levels of catecholamine’s and increased pain sensitivity, and may play a role in persistent pain after surgery.

• Different combinations of COMT SNPs (rs6269, rs4633, rs4818 and rs4680) define distinct haplotypes that have been found to be predictive of specific levels of pain response.

• Genetic variations of pro-inflammatory cytokines such as IL-1 receptor antagonist and IL-6 have been shown to affect pain sensitivity.
There is a significant genetic variation effect on opioid-related respiratory depression, nausea and drug disliking.

The most studied genetic variation in the OPRM1 receptor gene is the A118G SNP, with increased postoperative opioid requirements and reduced side effects reported in the GG homozygotes compared with the AA genotypes, although the observation has not been consistent.
• Genetic variations of pro-inflammatory cytokines such as IL-1 receptor antagonist and IL-6 have been shown to affect pain sensitivity.

• Pain sensitivity appears to differ among the genders, races, and ethnicity.

• The frequency of OPRM1 polymorphisms is approximately 46% among Asians, but only 5 and 25% in European and African–Americans populations.

• Ancestry information markers could be used to identify differences in allele frequency between populations from different geographical regions.

• The family history of substance abuse is allied with a higher risk for opioid addiction and genetic susceptibility namely in polymorphism of the μ-opioid receptor gene (OPRM1) and dopamine receptor gene (DRD1).
Table 1. Selected post-operative and chronic pain studies assessing polymorphisms in opioid receptor genes and opioid response.

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Gene</th>
<th>Variant</th>
<th>Study population</th>
<th>Route</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental pain studies</td>
<td>Morphine</td>
<td>OPRM1</td>
<td>A118G</td>
<td>102 surgical patients</td>
<td>IV/PCA No difference in pain scores or dose requirement. Decreased sedation and nausea.</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>OPRM1</td>
<td>A118G</td>
<td>80 female surgical patients</td>
<td>IV/PCA Increased morphine dose requirements. No difference in pain scores</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>OPRM1</td>
<td>A118G</td>
<td>120 surgical patients</td>
<td>IV/PCA Increased dose requirements. No difference in pain scores</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>OPRM1</td>
<td>A118G</td>
<td>588 female surgical patients</td>
<td>IV/PCA Increased dose requirements and pain scores. Decreased nausea/vomiting</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>OPRM1</td>
<td>A118G</td>
<td>189 surgical patients</td>
<td>IV/PCA Increased dose requirements. No difference in nausea and vomiting scores</td>
<td>59</td>
</tr>
<tr>
<td>Clinical pain studies</td>
<td>Morphine</td>
<td>OPRM1</td>
<td>A118G, -172G&gt;T, IVS2+310G&gt;A, IVS2-291G&gt;C</td>
<td>207 [99] cancer patients</td>
<td>NA Increased dose requirements (A118G only)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>OPRM1</td>
<td>A118G</td>
<td>137 cancer patients</td>
<td>Various Decreased pain relief</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>OPRM1, OPRK1 and OPRD1</td>
<td>Various</td>
<td>2294 cancer patients</td>
<td>Various No difference in opioid dose requirements</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Tramadol</td>
<td>OPRM1</td>
<td>A118G</td>
<td>160 patient with pain from knee osteoarthritis</td>
<td>Oral Decreased nausea and vomiting</td>
<td>55</td>
</tr>
</tbody>
</table>


Copyright © by British Pain Society
EPIGENETICS

• Epigenetics is the study of changes in the DNA methylation and modifications of histones or its supporting proteins at the molecular level

• Epigenetic mechanisms influence gene function without changing the original DNA sequence

• Pain response can be influenced by the environment, which in turn can affect the child’s DNA or supporting proteins.

• Developing research in pain epigenetics is imparting exactly how individuals are susceptible to chronic pain, and discovering novel genetic markers for pain drug therapies
IDENTIFYING CYP GENETIC POLYMORPHISMS

• Roche AmpliChip: FDA-Approved
• Blood sample
• Other MIRNA (gene expression)
• Transcriptomics (gene transcripts)
• Metabonomics (metabolites- “liver profiling”)
PHARMACOGENETICS AND PHARMACOGENOMICS KNOWLEDGE BASE (PHARMGKB)

• Publicly accessible knowledge base
  • www.pharmgkb.org

• Goal: establish the definitive source of information about the interaction of genetic variability and drug response
  1. Store and organize primary genotyping data
  2. Correlate phenotypic measures of drug response with genotypic data
  3. Curate major findings of the published literature
  4. Provide information about complex drug pathways
  5. Highlight genes that are critical for understanding pharmacogenomics
"Here's my sequence..."
REFERENCES


REFERENCES


Stevens et al. (2013) Pediatric perspective on pharmacogenomics. Pharmacogenomics, 14, 1889-1912

